Limitations to Treatment Safety and Efficacy

ADHERENCE TO ANTIRETROVIRAL THERAPY (Updated November 3, 2008)

Adherence to antiretroviral therapy (ART) has been strongly correlated with HIV viral suppression, reduced rates of resistance, an increase in survival*, and* improved quality of life *[1-2]*. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team. This section of the guidelines provides clinicians with a basis to approach the challenging and complicated topic of adherence.

Predictors of Adherence

Adherence is related to characteristics of the patient, the regimen, the clinical setting, and the relationship of the provider and the patient *[3]*. To assure adherence, it is critical that the patient receive and understand information about HIV disease and the specific regimen prescribed. A number of factors have been associated with poor adherence, including the following:

- low levels of literacy *[4]*;
- certain age-related challenges (e.g., vision loss, cognitive impairment) *[5]*;
- psychosocial issues (e.g., depression, homelessness, inadequate social support, stressful life events, dementia, or psychosis) *[6]*;
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma *[7];*
- difficulty taking medication (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., pill burden, dosing frequency, food requirements);
- adverse drug effects; and
- treatment fatigue.

Adherence studies in the early era of combination ART with unboosted protease inhibitors (PIs) found that taking 95% or more of doses was required for full viral suppression *[8]*. More recent adherence studies that utilized boosted PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) suggest that boosted PIs and efavirenz (EFV) may be more forgiving of lapses in adherence because of their longer half-lives *[9-10]*. Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses for all antiretroviral (ARV) regimens.

Measurement of Adherence

There is no gold standard for the assessment of adherence *[1],* but there are many validated tools and strategies to choose from. Although patient self-report of adherence predictably overestimates adherence by as much as 20% *[11]*, this measure still is associated with viral load responses *[12]*. Thus, a patient's report of suboptimal adherence is a strong indicator of nonadherence and should be taken seriously.

When ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses, patient self-report remains the most useful method for the assessment and longitudinal monitoring of a patient's adherence in the clinical setting. A survey of all doses during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice *[1]*. Other strategies may also be effective. One study found that asking patients to rate their adherence on a six-point scale during 1 month was more accurate than asking them how often they miss doses or asking about the percentage of doses taken during the previous 3 or 7 days *[13]*. Pharmacy records and pill counts also can be used as an adjunct to simply asking the patient *[14]*. Other methods of assessing adherence include the use of electronic measurement devices (e.g., bottle caps, dispensing systems). However, these methods may not be feasible in some clinical settings.

Interventions to Improve Adherence

Prior to writing the first prescriptions, the clinician should assess the patient's readiness to take medication, factors that might limit adherence (psychiatric illness, active drug use, etc.) that may require additional support, understanding of the disease and the regimen, social support, housing, work and home situation, and daily schedules. Patients should understand that the first regimen is usually the best chance for a simple regimen with long-term treatment success and prevention of drug resistance. Resources individualized to each patient's schedule, competing psychosocial needs, learning needs, and literacy level should be identified to foster adherence.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan *[14]*. The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit *[15-16]*. Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. With the patient who is not critically ill, several office visits and the patience of clinicians are generally required before therapy can be started.

A growing menu of possible interventions has demonstrated efficacy in improving adherence to ART. For example, a meta-analysis of 19 randomized controlled trials of ARV adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions *[17]*. Interventions that have been successful include those focused on the patient and those that work to improve the tolerability of the regimen. Successful support interventions of different modalities have included the following: adherence support groups, peer adherence counselors, behavioral interventions, cognitive-behavioral and reminder strategies, and use of community-based case managers and peer educators. Health care team members, such as nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs *[18-21]*. It is also important to address the competing needs of a patient, including active substance use, depression, and housing issues, to reduce the risk of nonadherence.

A number of advances during the past several years have dramatically simplified many regimens, particularly for ART-naïve patients. Prescribing regimens that are simple to take, have a low pill burden and frequency of dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence. Current treatment recommendations take regimen simplicity as well as efficacy into account.

Adherence assessment and counseling should be done at each clinical encounter and should be the responsibility of the entire health care team. Directly observed therapy (DOT) has been shown to be effective in provision of ART to active drug users *[22]*. In resource-limited settings, the use of community-based DOT has been very successful, and programs have replicated this intervention with success in the United States *[23]*. Although DOT is labor intensive and programmatically complex, modification of traditional DOT methodologies may be feasible and can be adapted in a variety of clinical settings, in which DOT is given a few days each week *[24]*.

Conclusion

Significant progress has been made regarding determinants, measurements, and interventions to improve adherence to ART. Given the various assessment strategies and potential interventions available, the challenge for the treatment team is to select the techniques that provide the best fit for their treatment setting, resources, and patient population. The complexity of this topic and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to prevent nonadherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can greatly reduce the development of viral resistance and the likelihood of virologic failure.

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Use a multidisciplinary team approach Provide an accessible, trusting health care team	• Nurses, social workers, pharmacists, and medication managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk of relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in antiretroviral (ARV) regimen selection	• For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Use a simple checklist the patient can complete in the waiting room • Have other members of the health care team also assess adherance • Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines.*)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers (see list above)
Assess and simplify regimen, if possible	

References

1. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S149-155.
2. World Heath Organization (WHO). Adherence to long term therapies – evidence for action. 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
3. Schneider J, Kaplan SH, Greenfield S, et al. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med.* 2004;19(11):1096-1103.
4. Marcus EN. The silent epidemic--the health effects of illiteracy. *N Engl J Med.* 2006;355(4):339-341.
5. van Eijken M, Tsang S, Wensing M, et al. Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. *Drugs Aging.* 2003;20(3):229-240.
6. Halkitis PN, Shrem MT, Zade DD, et al. The physical, emotional and interpersonal impact of HAART: exploring the realities of HIV seropositive individuals on combination therapy. *J Health Psychol.* 2005;10(3):345-358.
7. Carr RL, Gramling LF. Stigma: a health barrier for women with HIV/AIDS. *J Assoc Nurses AIDS Care.* 2004;15(5):30-39.
8. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
9. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis.* 2006;43(7):939-941.
10. Raffa JD, Tossonian HK, Grebely J, et al. Intermediate highly active antiretroviral therapy adherence thresholds and empirical models for the development of drug resistance mutations. *J Acquir Immune Defic Syndr.* 2008;47(3):397-399.
11. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis.* 2001;33(8):1417-1423.
12. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006;10(3):227-245.
13. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav.* 2008;12(1):86-94.
14. Bieszk N, Patel R, Heaberlin A, et al. Detection of medication nonadherence through review of pharmacy claims data. *Am J Health Syst Pharm.* 2003;60(4):360-366.
15. Vermeire E, Hearnshaw H, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26(5):331-342.
16. Williams A, Friedland G. Adherence, compliance, and HAART. *AIDS Clin Care.* 1997;9(7):51-54, 58.
17. Simoni JM, Pearson CR, Pantalone DW, et al. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S23-35.
18. McPherson-Baker S, Malow RM, Penedo F, et al. Enhancing adherence to combination antiretroviral therapy in non-adherent HIV-positive men. *AIDS Care.* 2000;12(4):399-404.
19. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. *J Assoc Nurses AIDS Care.* 2005;16(5):3-15.
20. Remien RH, Stirratt MJ, Dognin J, et al. Moving from theory to research to practice. Implementing an effective dyadic intervention to improve antiretroviral adherence for clinic patients. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S69-78.
21. Mannheimer SB, Morse E, Matts JP, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S41-47.
22. Altice FL, Maru DS, Bruce RD, et al. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis.* 2007;45(6):770-778.
23. Behforouz HL, Kalmus A, Scherz CS, et al. Directly observed therapy for HIV antiretroviral therapy in an urban US setting. *J Acquir Immune Defic Syndr.* 2004;36(1):642-645.
24. Goggin K, Liston RJ, Mitty JA. Modified directly observed therapy for antiretroviral therapy: a primer from the field. *Public Health Rep.* 2007;122(4):472-481.